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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,266	09/25/2003	Byung Sook Moon	020048-004200US	8805

20350 7590 09/17/2009

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PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
09/17/2009	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/672,266
Filing Date: September 25, 2003
Appellant(s): MOON ET AL.

Alexander R. Trimble
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on May 6, 2009 and June 29, 2009 appealing from the Office action mailed April 8, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,861,251	Park et al.	1-1991
5763157	Treml et al.	6-1998

Kellogg et al. (1994) Biotechniques Vol. 16 (6) 1134-1137.

Shively et al. March 2003 BioTechniques vol. 34: (3) pp. 498-504.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-10, 12, 45-48, 50-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Regarding claims 1 and 45 applicant has added the limitation "substantially spherical". Examiner could not find even a single instance in the specification where term substantial or substantially was used in context of the spherical lyophilized beads. Therefore a NEW MATTER rejection is being made for claims 1 and 45. Claims 2-10, 12, 46-48, 50-53 depend from claims 1 and 45. Hence the NEW MATTER rejection applies to claims 1-10, 12, 45-48, and 50-53.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-7, 10, 12, 45-48, 52-53, 63 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. 1999 US Pat. 5,861,251 in view of Treml et al. 1998 US Pat. 5,763,157.

Claims 1, 45, 63 and 64 are being considered together because claims 45 and 64 are a product by process claim that shares the same structural components namely lyophilized bead suitable for use in amplification of a nucleic acid comprising a thermally stable enzyme and mannitol as recited in product of claims 1 and 63. The process steps (a-c in claim 45) are not being considered for search of prior art. See MPEP 2113 [R1] PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

A) Regarding claims 1, 7, 45, 48, 63 and 64 Park et al. teach:

a. A lyophilized reagent suitable for use in the amplification of a nucleic acid sequence, (see col. 1, lines 5-10, and col. 3, lines 1-10)

b. said lyophilized reagent comprising: a thermally stable enzyme (see col. 3, lines1-10). Park et al. teach use of DNA Polymerase as the enzyme used for conducting amplification of nucleic acid using polymerase chain reaction where the enzyme is subjected to repeated cycling at high temperatures up to 94^{o}C. Hence the DNA polymerase used by them is thermally stable as it successfully performs DNA amplification as shown in examples 1-8 (see col. 3, lines 66-67; col. 4, 5 and 6 lines 1-67 of each).

c. And mannitol (see col. 3, line 27). Park et al. use mannitol as a stabilizer. Mannitol is part of their preferred stabilizers falling in the group of polyols composed of glycerol, glucose, mannitol, galacitol, glucitol and sorbitol (see col. 3, lines 24-30).

Regarding claim 2, Park et al. teaches amplification in a reaction mixture having a final volume of 50 µl (see col. 4, lines12-13 and lines 47-52).

Regarding claims 3 and 47, Park et al. teaches dNTPs (see col.4, line 11) and mixture of ddNTPs and dNTPs (see col. 3, lines 1-10).

B) Regarding claims 1, 45, 63 and 64 Park et al. do not teach:

d. A lyophilized bead wherein said lyophilized bead has a weight percentage of said mannitol of between about 53% and about 75% (w/w).

C) Regarding claims 1, 5-6, 45, 63 and 64 Treml et al. teach:

e. A lyophilized bead referred to as biological reagent spheres by Treml et al. suitable for use in the amplification of a nucleic acid sequence (see col. 3, lines 60-67; col. 4, lines 1-8 & col. 7, lines 23-35).

In case of Treml et al. these beads are composed of a high molecular weight synthetic carbohydrate polymer and a second carbohydrate. Examples of second carbohydrate used by Treml et al. includes polyols such as sorbitol. The lyophilized beads with weight percentage of second carbohydrate in the range of 5% to 15% expressed in (w/v) are taught by Treml et al. (see col. 5, lines 49-52). Treml et al. does not express the weight percentage of polyol in the beads in (w/w).

During interview of June 4, 2007 consensus was reached that the range disclosed by Treml et al. would be about 45% (w/w).

The range claimed by Applicant is between about 53% and about 75%. Since upper limit is about 75% and lower limit is about 53%, hence this claimed range includes a variance of (75-53/2 = 22/2= 11) +/- 11%. So the lower limit of the claimed range is 53 – 11 = 42%.

The lyophilized beads of claims 1, 5, 6, 63 having weight percentage of between about 53% and about 75% (w/w) as recited in claims 1 and 63; weight percentage of lyophilized bead between about 62% and about 75% (w/w) as recited in claim 5; and weight percentage of lyophilized bead between about 68% and about 75% (w/w) as recited in claim 6 are taught by Treml et al. because the compositions of Treml et al. were shown to contain about 45% (w/w) polyol. As shown above by Examiner, the % taught by prior art Treml et al., 45% falls within the lower limit of the range claimed by applicant 42%.

Thus, an ordinary practitioner would have recognized that the results optimizable variables of concentration of mannitol could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific mannitol concentration was other than routine, that the products resulting from the optimization have any unexpected claimed properties, or that the beads made by the instant invention should be considered unexpected in any way with reference to their suitability for amplification of nucleic acid as compared to the closest prior art.

Regarding new limitation added to amended base claim 1 and 45 that recites lyophilized beads "being substantially spherical in shape". Applicant has not defined "substantially spherical" in the specification. Fig. 1 part A of the specification shows

beads that are made with 9% w/v =72% w/w of Trehalose. To the Examiner these beads shown in Fig. 1 A, appear to be "substantially spherical in shape". Based on this Examiner concludes, since lyophilized beads made with sugars other than mannitol and having w/w percentages that are within the claimed range are also "substantially spherical in shape".

Therefore the lyophilized beads taught by Park and Treml et al. will necessarily meet the newly added limitation i.e. they will also be "substantially spherical in shape".

Regarding claims 4 and 46, Treml et al. teaches reagent spheres (lyophilized beads) with diameters of about 2 mm to about 6 mm. Preferably, the reagent sphere has a diameter of about 2.5 mm (see col. 3, lines 63-65). Thus lyophilized bead with an average cross-section of about 1 mm and about 4.5 mm are taught by Treml et al.

Regarding claims 10 and 52, Treml et al. teaches reagent spheres where the biological reagents are oligonucleotides, proteins, enzymes, DNA or nucleic acids (see co. 4, lines 7-8). All of these are employed as probes in the art for different purposes.

Regarding claims 12 and 53, Treml et al. teaches reagent spheres where the biological reagent is selected from at least one of the group consisting of DNA/RNA modifying enzymes, restriction enzymes, nucleotides, oligonucleotides, proteins, enzymes, DNA or nucleic acids (see col. 4, lines 4-8). Different molecules may be used as internal control for different purposes. For example DNA could be used as internal control for amplification reactions, therefore Treml et al. teaches a bead containing internal control.

As described above Park et al specifically teach use of mannitol as a preferred polyol to be used for stabilizing lyophilized reagents to be used for nucleic acid amplification.

Hence it would have been obvious to one of ordinary skill in the art at the time of the present invention to use the lyophilized beads of Treml et al. as the lyophilized reagent of Park et al. for use in nucleic acid amplification. The motivation to use lyophilized beads as described by Treml et al. as lyophilized reagent useful for amplification of nucleic acid taught by Park et al. is provided by Treml et al. who describe the limitations and drawbacks associated with the various methods such as dry-blending, spray drying, freeze drying, fluidized bed drying, and /or cryogenic freezing employed for producing dry biological reagents (see col. 1, lines 32-67; col. 2, lines 1-25; col. 3, lines 1-22). They further go on to describe the advantages of their invention namely "providing a homogenous solution of biological reagent(s), glass forming filler material, and water-wherein the shape of droplets formed on an inert cryogenic surface can be controlled by changing the percent solids of emulsion ---------- providing stable storage of a biological reagent that would otherwise be unstable when alone in an aqueous solution at room temperature and providing stable storage of a plurality of biological reagents that would otherwise react with each other when in an aqueous solution at room temperature" (see col.4, lines 51-67 and col. 5, lines 1-9).

9. Claims 8 and 50, are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. and Treml et al. as applied to claims 1 and 45 above, and further in view of Kellogg et al. (1994) Biotechniques Vol. 16 (6) 1134-1137.

Regarding claims 8 and 50, Park et al. and Treml et al. teach the bead of claim 1 and 45 but they do not teach a component selected from the group consisting of an antibody that inactivates a polymerase and a wax or oil to sequester magnesium.

Regarding claims 8 and 50, Kellogg et al. teach an antibody that inactivates a polymerase (see page 1135, par. 3 where a Taq DNA Polymerase that when coupled to neutralizing TaqStartAntibody™, a monoclonal antibody (MAb) directed against Taq DNA polymerase facilitates "Hot start" PCR is taught)

It would have been prima facie obvious to one of ordinary skill in the art to incorporate the Taq DNA Polymerase coupled to neutralizing TaqStartAntibody™, of Kellogg et al. in the product of Park et. al. and Treml et al. at the time the invention was made. The motivation to combine the product of Kellogg et al. in the product of Park et al. and Treml et al. is provided by Kellogg et al. who state "To address the drawbacks inherent in the above methods, we have generated the TaqStartAntibody™, a monoclonal antibody (MAb) the deactivates Taq DNA polymerase at ambient temperature. Heating a reaction mixture to the denaturation temperature reverses the deactivation of the polymerase and permits the amplification to proceed in a specific and efficient manner. The results indicate that using the antibody greatly reduces non specific products and enhances yield of the specific product" (see page 1135, par. 3).

10. Claims 9 and 51, are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. and Treml et al. as applied to claims 1 and 45 above, and further in view of Shively et al. March 2003 BioTechniques vol. 34: (3) pp. 498-504.

Regarding claims 9 and 51, Park et al. teaches a reaction buffer (see col. 2, line 1) that must be part of the reaction mixture before amplification of nucleic acids can take place by PCR. But neither Park et al. nor Treml et al. teaches use of buffer N-(2-Hydroxyethyl) piperazine-N'-(2-ethanesulfonic acid) (HEPES) in DNA amplification.

Shively et al. teaches use of HEPES buffer in amplification reactions used to perform Real –Time PCR assay for quantitative mismatch detection. (see page 498 abstract). They describe an assay suitable for quantitative detection of single-base-pair differences that does not require fluorescently labeled gene specific probes. The method requires use of HEPES buffer at a pH of 6.95 together with Ampli-Taq^{R} DNA polymerase results in a threshold difference between the correct template and the mismatched template of as many as 20 cycles, depending on the mismatch. (see page 498, abstract).

It would have been obvious to one of ordinary skill in the art to incorporate the buffer of Shively et al. in the product of Park et al. and Treml et al. The motivation to combine the buffer of Shively et al. in the product of Park et al. and Treml et al. is provided by Shively et al. who state " the technique we describe allows more accurate quantification because the buffer we utilize results in greater allele-specific differences in threshold cycles (see page 499, par. 1)" and "It was necessary to use HEPES buffer, pH 6.95, instead of the standard Tris-HCl, pH 8.3, for mismatch discrimination at the level shown in Figure 2". (see page 502, par. 3).

(10) Response to Argument

Re: Independent claims 1 and 45 along with dependent claims 2-10, 12, 46-48 and 50-53 rejected under 35 U.S.C. § 112, 1st, as failing to comply with the written description requirement in view of the amendment to claims 1 and 45 adding the limitation "substantially spherical."

Appellant's arguments filed May 6, 2009 have been fully considered but they are not persuasive. Appellant argues that there is sufficient written description for the limitation "substantially spherical". Examiner disagrees because:

Regarding claims 1 and 45 applicant recites the limitation "substantially spherical". Appellant has not defined "substantially spherical" in the specification. Fig. 1 part A of the specification shows beads that are made with 9% w/v =72% w/w of Trehalose. To the Examiner these beads shown in Fig. 1 A appear to be "substantially spherical in shape". Based on this, Examiner concludes lyophilized beads made with sugars other than mannitol and having w/w percentages that are within the claimed range of mannitol are also "substantially spherical in shape".

Therefore the lyophilized beads taught by Park and Treml meet the limitation, i.e., they will also be "substantially spherical in shape". Hence Examiner concludes that the cited art is still applicable and the amendment is not sufficient to overcome the cited art.

In addition, Examiner searched the instant specification as filed to find support for the newly added limitation, namely "substantially spherical". Examiner did not come across a single instance where the term "substantially" was used in this context. Hence Examiner did a written description new matter rejection to indicate the above fact.

Therefore a NEW MATTER rejection for claims 1 and 45 is still valid. Claims 2-10, 12, 46-48, 50-53 depend from claims 1 and 45. Hence the NEW MATTER rejection of claims 1-10, 12, 45-48, and 50-53 is still valid and is being maintained.

Re : B.Independent claims 1, 45, 63 and 64, along with dependent claims 2-7, 10, 12, 46-48 and 52-53 rejected under 35 U.S.C. § 103(a) as being obvious over Park et al. (U.S. Patent No. 5,861,251) in view of Treml et al. (U.S. Patent No. 5,763,157)

Appellant's arguments filed May 6, 2009 have been fully considered but they are not persuasive.

Appellant argues that neither Park et al. nor Treml et al. teach a bead that is substantially spherical. Examiner disagrees because regarding claims 1 and 45 applicant recites the limitation "substantially spherical". Appellant has not defined "substantially spherical" in the specification. Fig. 1 part A of the specification shows beads that are made with 9% w/v =72% w/w of Trehalose. To the Examiner these beads shown in Fig. 1 A, appear to be "substantially spherical in shape". Based on this, Examiner concludes lyophilized beads made with sugars other than mannitol and having w/w percentages that are within the claimed range of mannitol are also "substantially spherical in shape". Therefore the lyophilized beads taught by Park and Treml meet the limitation, i.e., they will also be "substantially spherical in shape". Hence Examiner concludes that the cited art is still applicable and the amendment is not sufficient to overcome the cited art.

Appellant correctly argues that Park et al. do not teach a bead having mannitol between about 53% and about 75% (w/w) of the bead. Examiner has used Park et al. to

only teach a bead having mannitol. Examiner has used Treml et al. to teach the claimed concentration of between about 53% and about 75% (w/w) of the bead.

Appellant further argues that Treml et al. does not teach the claimed composition of 53% (w/w). Examiner disagrees. During the interview of June 4, 2007 consensus was reached that the range disclosed by Treml would be about 45% (w/w).

The range claimed by Appellant is between about 53% and about 75%. Since the upper limit is about 75% and lower limit is about 53%, this claimed range includes a variance of (75-53/2 = 22/2= 11) +/- 11%. So the lower limit of the claimed range is 53 – 11 = 42%.

The lyophilized beads of claims 1, 5, 6, 63 having a weight percentage of between about 53% and about 75% (w/w) as recited in claims 1 and 63; weight percentage of lyophilized beads between about 62% and about 75% (w/w) as recited in claim 5; and weight percentage of lyophilized beads between about 68% and about 75% (w/w) as recited in claim 6; are taught by Treml et al. because the compositions of Treml et al. were shown to contain about 45% (w/w) polyol. As shown above by Examiner, the percentage taught by the prior art Treml et al., 45%, falls within the lower limit of the range claimed by Appellant (42%).

Thus, an ordinary practitioner would have recognized that the results optimizable variables of concentration of mannitol could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific mannitol concentration was other than routine, that the products resulting from the optimization have any unexpected claimed properties, or that the beads used in the instant invention should be considered unexpected in any way with reference to their suitability for amplification of nucleic acid as compared to the closest prior art. This is the basis for why Examiner concludes the prior art cited is valid and does teach the recited concentration range.

Finally Appellant argues that the Jones declaration describes unexpected and surprising results for the lyophilized mannitol beads of the present invention. This declaration has been fully considered but is not found to be persuasive.

Response to Applicant's submission of 37 CFR 1.132 Declaration

The declaration by Martin Jones under 37 CFR 1.132 filed on July 12, 2007 is insufficient to overcome the rejection of claims 1-8, 10, 12, 45-48, 50 and 52-53 based upon Park and Treml as set forth in the last Office action because: The declaration filed by Martin Jones provides details of unexpected results, but the unexpected results described in the declaration from paragraphs 5-9 are related to features of lyophilized "crystalline beads" that are not recited in the instant claims.

Paragraph 5 refers to "beads that are reproducibly spherical with a smooth morphology". Appellant is reminded that the language "reproducibly spherical with a smooth morphology" is not recited anywhere in the instant claims.

Paragraph 7 refers to properties associated with "crystalline beads". Examiner would like to point out that the structural limitation "crystalline beads" is not part of the current claim language.

Paragraph 8 refers to "reproducibility and homogeneity" of the size of the beads. Examiner would like to point out that the structural limitation "reproducibility and homogeneity" is not part of the current claim language.

Hence the unexpected results provided in the Jones declaration relate to features that are not recited in the instant claim language, and are insufficient to overcome the rejection of claims 1-8, 10, 12, 45-48, 50 and 52-53 based upon Park and Treml as set forth in the last Office action. Hence these are being maintained.

C. Re rejection of Dependent claims 8 and 50 were rejected under 35 U.S.C. § 103(a) as being obvious over Park et al. (U.S. Patent No. 5,861,251) in view of Treml et al. (U.S. Patent No. 5,763,157) as applied to claims 1 and 45, and further in view of Kellogg et al. Biotechniques 1994, 16(6), 1134-1137.

Since the 103 (a) rejection of claims 1 and 45 over Park and Treml has been maintained, the rejection further in view of the secondary reference Kellogg et al. is also being maintained.

D. Re rejection of Dependent claims 9 and 51 were rejected under 35 U.S.C. § 103(a) as being obvious over Park et al. (U.S. Patent No. 5,861,251) in view of Treml et al. (U.S.Patent No. 5,763,157) as applied to claims 1 and 45, and further in view of Shively et al. Biotechniques 2003, 34(3), 498-504.

Since the 103 (a) rejection of claims 1 and 45 over Park and Treml has been maintained, the rejection further in view of the secondary reference Shively et al. is also being maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Suchira Pande, Examiner

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